



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale?

Citation for published version:

Weir, J, Steyerberg, EW, Butcher, I, Lu, J, Lingsma, HF, McHugh, G, Roozenbeek, B, Maas, AIR & Murray, GD 2012, 'Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale?', *Journal of Neurotrauma*, vol. 29, no. 1, pp. 53-8. <https://doi.org/10.1089/neu.2011.2137>

Digital Object Identifier (DOI):

[10.1089/neu.2011.2137](https://doi.org/10.1089/neu.2011.2137)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Journal of Neurotrauma

Publisher Rights Statement:

Copyright 2012, Mary Ann Liebert, Inc. Available via Europe PubMed open access link

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



Does the Extended Glasgow Outcome Scale Add Value to the Conventional Glasgow Outcome Scale?

James Weir,¹ Ewout W. Steyerberg,² Isabella Butcher,¹ Juan Lu,³ Hester F. Lingsma,² Gillian S. McHugh,¹ Bob Roozenbeek,^{2,4} Andrew I.R. Maas,⁴ and Gordon D. Murray¹

Abstract

The Glasgow Outcome Scale (GOS) is firmly established as the primary outcome measure for use in Phase III trials of interventions in traumatic brain injury (TBI). However, the GOS has been criticized for its lack of sensitivity to detect small but clinically relevant changes in outcome. The Glasgow Outcome Scale-Extended (GOSE) potentially addresses this criticism, and in this study we estimate the efficiency gain associated with using the GOSE in place of the GOS in ordinal analysis of 6-month outcome. The study uses both simulation and the reanalysis of existing data from two completed TBI studies, one an observational cohort study and the other a randomized controlled trial. As expected, the results show that using an ordinal technique to analyze the GOS gives a substantial gain in efficiency relative to the conventional analysis, which collapses the GOS onto a binary scale (favorable versus unfavorable outcome). We also found that using the GOSE gave a modest but consistent increase in efficiency relative to the GOS in both studies, corresponding to a reduction in the required sample size of the order of 3–5%. We recommend that the GOSE be used in place of the GOS as the primary outcome measure in trials of TBI, with an appropriate ordinal approach being taken to the statistical analysis.

Key words: clinical trial; Glasgow Outcome Scale-Extended; Glasgow Outcome Scale; ordinal analysis; outcome; traumatic brain injury

Introduction

THE GLASGOW OUTCOME SCALE (GOS) was developed by Jennett and Bond (1975), and has since become firmly established as the primary outcome measure used in the majority of Phase III trials in traumatic brain injury (TBI). Unfortunately the development of interventions to treat TBI has been hugely disappointing. In spite of very promising preclinical data on a range of neuroprotective agents, none of the major Phase III trials reported to date have shown convincing evidence of effectiveness over a broad class of TBI patients (Maas et al., 2010). The reasons why the results have been so disappointing have been widely debated, and one possible explanation is that the GOS lacks the sensitivity to detect small but clinically relevant treatment effects.

In response to the perceived lack of sensitivity of the GOS, Jennett and associates (1981) developed the GOSE, an extended version of the GOS. While in principle the extended scale should offer greater sensitivity to detect changes in outcome, potential gains could be lost if the extended scale

introduces more inter-observer variability. The aim of this article is to evaluate whether the GOSE adds value to the GOS as an outcome measure in head injury trials.

The Glasgow Outcome Scales

The original Glasgow Outcome Scale has five ordered categories: Death, Vegetative State, Severe Disability, Moderate Disability, and Good Recovery. Although the GOS has been widely adopted as the preferred instrument for assessing outcome after TBI, it has been subject to criticism over the years (Anderson et al., 1993; Gouvier et al., 1986; Hall et al., 1985; Maas et al., 1983). It can be argued that five outcome categories are too few to represent the wide range of mental and physical handicaps a patient can suffer following TBI.

The GOSE scale splits each of Severe Disability, Moderate Disability, and Good Recovery into lower and upper categories to allow for greater differentiation between the levels of recovery that can be achieved. Several other extended scales have been suggested in the past, but have not been widely

¹Centre for Population Health Sciences, University of Edinburgh, Edinburgh, United Kingdom.

²Department of Public Health, Centre for Medical Decision Making, Erasmus MC, Rotterdam, The Netherlands.

³Department of Neurosurgery, Virginia Commonwealth University Medical Center, Richmond, Virginia.

⁴Department of Neurosurgery, Antwerp University Hospital, Edegem, Belgium.

adopted (Horne and Schemitsch, 1989; Livingston and Livingston, 1985; Maas et al., 1983; Smith et al., 1979).

Traditionally, TBI trials have been analyzed by grouping the GOS into two categories: Unfavorable (Death, Vegetative State, or Severe Disability) versus Favorable (Moderate Disability or Good Recovery). Such a dichotomization of an ordinal scale discards potentially relevant information (Altman and Royston, 2006), and in particular in our context would abolish any distinction between the GOS and the GOSE. Recent work reported by the IMPACT group (McHugh et al., 2010) has shown that appropriate statistical methods can be applied to analyze the full ordinal GOS scale, leading to an analysis which substantially increases the statistical efficiency. For a given sample size, an ordinal analysis can detect a smaller treatment effect than can be done using conventional dichotomous analysis. Thus in this paper we evaluate whether ordinal analysis of the GOSE leads to further efficiency gains over and above ordinal analysis of the GOS.

The IMPACT database

This work was undertaken by the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) group and was funded partly by the U.S National Institutes of Health. The IMPACT group is a collaboration of researchers from Belgium, The Netherlands, the U.K. and the U.S.A. See <http://www.tbi-impact.org/> for more information, or Maas and associates (2010) for a broad overview of the IMPACT work to date.

The IMPACT study group has dedicated significant resources to collating data from various TBI studies into one large database. Not all of the studies used the same formats for recording information, so merging the data was not straightforward. Currently the database contains data on almost 12,000 patients. This is a combination of four observational studies and 11 randomized controlled trials (RCTs). The development of the IMPACT database has been described by Marmarou and colleagues (2007).

This particular analysis is based on two of the studies in the IMPACT database with GOSE data available (Table 1). The APOE study (Teasdale et al., 2005) was a cohort study with patients recruited from consecutive head injury admissions to the regional Neurosurgical Unit for the West of Scotland. The study was designed to investigate the hypothesis that possession of the APOE $\epsilon 4$ allele is associated with poorer outcome after acute head injury. The PHARMOS study (Maas

et al., 2006) was an international multi-center randomized clinical trial that evaluated the efficacy and safety of dexamethasone in severe TBI.

Methods

Ordinal analysis

In this study we use two ordinal analysis approaches which have been described in detail in previous IMPACT publications (Maas et al., 2010; McHugh et al., 2010). The proportional odds model (Bolland et al., 1998; McCullagh, 1980) in effect estimates the odds ratio associated with each potential dichotomy of an ordinal outcome scale, and leads to a pooled estimate, assuming that each odds ratio is equal to an overall common odds ratio. This estimated common odds ratio can be thought of as a measure of the shift of outcome over the entire ordinal scale that is associated with an intervention or a prognostic marker.

The sliding dichotomy approach is based on grouping patients into subgroups reflecting baseline risk, on the basis of a prognostic model. Within each prognostic group the median observed outcome category represents the expected outcome, and the impact of an intervention or a prognostic marker is evaluated in terms of its impact on increasing the proportion of outcomes which are better than would be expected, given the baseline prognostic risk. The estimated sliding dichotomy odds ratio can be thought of as a measure of how much outcome is better than expected over the entire ordinal scale in association with an intervention or a prognostic marker.

Both of these ordinal methods have been assessed using an extensive set of simulations and were found to be highly efficient in comparison to a basic dichotomization of the GOS (McHugh et al., 2010). Reductions in sample size of the order of 40% were shown, with the proportional odds model generally outperforming the sliding dichotomy approach. The authors found it difficult to recommend a method, as they both had their strong points: the proportional odds model produced the larger efficiency gains, but the sliding dichotomy had arguably more clinical appeal.

When using the GOS or GOSE in ordinal analyses it is generally accepted that the categories Death and Vegetative State should be pooled for statistical and clinical reasons. These include the fact that there are usually a low number of patients in the Vegetative State category, and also that Vegetative State could never be regarded as a favorable outcome, even if the baseline prognosis is strongly adverse. Therefore the GOS was reduced to a four-category outcome and the GOSE to a seven-category outcome. The conventional dichotomized GOS was included to act as a reference technique.

Statistical analysis

In order to compare the GOS and GOSE we used the previously mentioned PHARMOS and APOE datasets. For the PHARMOS study we investigated the sensitivity of the different approaches in estimating the effect of the randomized treatment, and for the APOE study the impact of possession of an $\epsilon 4$ allele was taken as the treatment effect. Two types of investigations were carried out: a standard error analysis and a simulation study. Patients with a missing outcome measure were not included in the analyses. Any children in the APOE study were also excluded. These exclusions gave us the

TABLE 1. DETAILS OF THE STUDIES USED IN THE ANALYSES

	APOE	PHARMOS
Study year	1996–1999	2001–2004
Study type	Cohort	RCT
Patients (<i>n</i>)	984	861
Age range (years)	0–93	16–66
Time window	N/A	≤6 h
Centers (<i>n</i>)	1	86
Mortality (%)	13	17
Unfavorable outcome (%)	34	51
Reference	Teasdale et al. (2005)	Maas et al. (2006)

RCT, randomized controlled trial.

following patient totals: PHARMOS ($n=856$) with an age range of 16–66 years, and APOE ($n=714$) with an age range of 16–93 years.

Standard error analysis. This method involved fitting different models for each outcome scale and examining the standard error of the estimated treatment effect. We expected to observe a decrease in the standard error as the number of categories in the outcome scale increased. There are potential problems in comparing standard errors for treatment effects in non-linear models (Ford and Norrie, 2002; Robinson and Jewell, 1991), with the counter-intuitive finding that covariate adjustment typically increases the standard error of an estimated treatment effect. However, in our context and under the assumption of proportional odds the binary logistic regression model and proportional odds models are estimating what is fundamentally the same parameter.

We used PROC LOGISTIC in SAS® to fit three different models (SAS 9.2, SAS System for Windows; SAS Institute Inc., Cary, NC). For both sets of data the models were fitted three times with increasing numbers of covariates: (1) No covariates + treatment variable; (2) Three covariates (age, Glasgow Coma Scale motor score, and pupillary reaction) + treatment variable; and (3) Seven covariates (age, Glasgow Coma Scale motor score, pupillary reaction, CT scan classification, traumatic subarachnoid hemorrhage, hypoxia, and hypotension) + treatment variable (Murray et al., 2007; Steyerberg et al., 2008).

Simulation study. The second analysis method involved running a series of simulations to investigate possible reductions in sample size for the four-category GOS and the seven-category GOSE, using a basic chi-squared analysis of the dichotomized GOS as the reference level. A detailed description of a similar simulation study can be found in McHugh and associates (2010). A summary of the steps involved is as follows.

- Simulate an outcome on the GOSE scale for 400 randomly-selected patients from the two datasets using their baseline data. This generates the placebo group.

- Repeat the same process for another 400 patients, but this time incorporating a treatment effect. The treatment effect was calibrated to ensure a 5% absolute increase in the proportion of patients with a favorable outcome. This step generates the intervention group.
- Each simulation scenario is repeated 1000 times and a reduction in sample size is calculated from the output. The scenarios are also analyzed for the four-category GOS, which is obtained by collapsing the GOSE.
- The simulation scenarios are different combinations of analysis methods and numbers of covariates. Methods include a chi-squared analysis for the dichotomous GOS, and proportional odds and sliding dichotomy analyses for the four- and seven-category scales.

The findings are expressed in terms of the percent reduction in sample size that can be achieved without loss of statistical power, as explained in detail by Hernandez and colleagues (2006).

Results

Standard error analysis

As expected (McHugh et al., 2010), there is a substantial efficiency gain when going from the conventional binary analysis to an ordinal analysis of the GOS (Table 2). There is then a further efficiency gain when going from the GOS to the GOSE. To quantify the difference between the outcome scales into a more meaningful measure, reductions in sample size have been calculated using the dichotomized GOS as the reference level. The four-category GOS shows a 20–40% reduction in sample size relative to the dichotomous analysis, depending on which model and dataset is used. The GOSE shows a modest but consistent gain over the four-category GOS, with a 23–43% reduction. We also note, as discussed earlier, that covariate adjustment leads to an increase in the standard error of the treatment effect.

Simulation study

Looking at the simulation study results (Fig. 1), we find that there are larger reductions in sample size in every simulation

TABLE 2. STANDARD ERROR OF THE TREATMENT EFFECTS AND THE ASSOCIATED REDUCTIONS IN SAMPLE SIZE (USING THE DICHOTOMIZED GOS AS THE REFERENCE LEVEL)

Model and outcome scale	PHARMOS			APOE		
	Estimated treatment effect	Standard error	Reduction in sample size (%)	Estimated treatment effect	Standard error	Reduction in sample size (%)
No covariate						
GOS (2 category)	0.0193	0.1368	Reference	0.0863	0.1617	Reference
GOS (4 category)	0.0498	0.1224	19.9	−0.0120	0.1424	22.4
GOSE (7 category)	0.0576	0.1200	23.1	0.0492	0.1403	24.7
3 Covariates						
GOS (2 category)	−0.0235	0.1432	Reference	0.3054	0.1895	Reference
GOS (4 category)	0.0369	0.1243	24.7	0.1342	0.1490	38.2
GOSE (7 category)	0.0508	0.1214	28.1	0.2079	0.1449	41.5
7 Covariates						
GOS (2 category)	−0.0113	0.1482	Reference	0.2929	0.1933	Reference
GOS (4 category)	0.0539	0.1258	27.9	0.1148	0.1502	39.6
GOSE (7 category)	0.0697	0.1223	31.9	0.1875	0.1454	43.4

GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale-Extended.

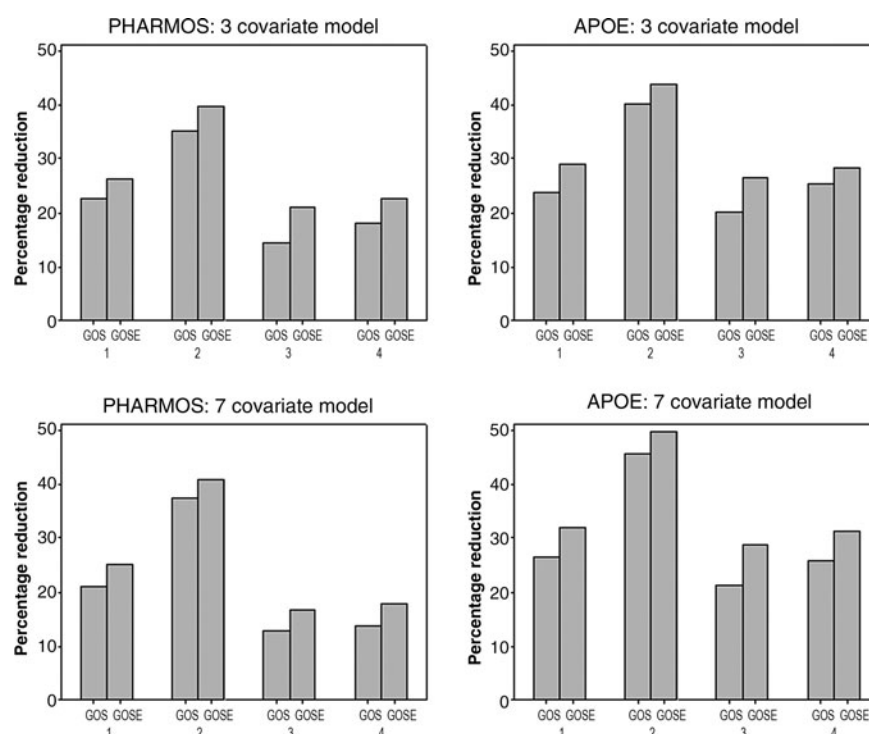


FIG. 1. Numbers 1 to 4 on the horizontal axis correspond to following methods: 1, proportional odds, treatment only; 2, proportional odds, treatment+covariates; 3, sliding dichotomy, treatment only; and 4, sliding dichotomy, treatment+covariates. “Treatment only” means that the final analysis model contained the treatment variable only, while “Treatment+covariates” means that the final analysis model contained the treatment variable plus covariates (3 or 7). See the statistical analysis section for a list of the covariates used. GOS, Glasgow Outcome Scale; GOS+SE, Glasgow Outcome Scale-Extended.

scenario when using the seven-category GOS compared to the four-category GOS. Tying in closely with the results from the standard error analysis, there is typically an additional 3–5% reduction in sample size when using the GOS compared to the GOS+SE. These gains are again over and above the substantial efficiency gain obtained when going from a binary analysis to an ordinal analysis of the GOS. Another clear finding is that the proportional odds approach tends to perform better than the sliding dichotomy approach, a pattern also seen by McHugh and colleagues (2010). It is also apparent in both Table 2 and Figure 1 that larger percentage reductions in sample size are achieved with the APOE study than with the PHARMOS trial in every scenario. This is again consistent with the findings of McHugh and colleagues (2010), that greater efficiency gains tended to be achieved in cohort studies with broad entry criteria than in randomized trials with tightly defined entry criteria.

Discussion

Two main conclusions may be drawn from our results. First, as has been shown previously (McHugh et al., 2010), it is clear that ordinal analysis of the four-category GOS yields substantial efficiency gains relative to the conventional dichotomous analysis. Second, using the seven-category GOS+SE gives modest but consistent efficiency gains over and above those achieved by the use of the four-category GOS. These additional gains correspond to a sample size reduction of the order of 3–5%. In our opinion such an additional gain easily

justifies the additional effort required to assess outcome using the full GOS+SE in place of the GOS.

In these analyses an important point we had to consider was how to collapse the eight-category GOS. We chose to group Death and Vegetative State together to form a seven-category scale. An alternative would have been to group Death, Vegetative State, and Lower Severe Disability together to form a six-category scale as used in the original analysis of the PHARMOS trial (Maas et al., 2006). In a sensitivity analysis we repeated the analyses described above using the six-category GOS+SE, and in general this approach was inferior to using the seven-category scale.

Ordinal analysis using the proportional odds model or the sliding dichotomy does require a greater degree of statistical sophistication than that required for a conventional binary analysis. However, this has not prevented such approaches from being used in practice (Maas et al., 2006; Sandset et al., 2011). An alternative approach to the analysis of the GOS has been suggested by Aoki and associates (1998). Based on interviews with doctors, nurses, and medical students, they assigned a numerical utility to each level of the GOS, allowing the ordinal scale to be mapped onto an interval scale relating to quality of life. It is not clear, however, whether this approach would achieve the efficiency gains that have been demonstrated for the proportional odds model and the sliding dichotomy.

Any potential efficiency gains that would result from an extended outcome scale could be lost if the inter-observer variability increases along with the length of the scale. In

order to address how best to assess the GOSE, Wilson and colleagues (1998) developed a set of structured interview questions. A study carried out by the same authors demonstrated kappa values of 0.89 for the GOS and 0.85 for the GOSE. In comparison to the results shown by Maas and associates (1983), there was a substantial improvement in the degree of inter-observer agreement when using the structured interview.

Further evidence in support of the GOSE can be found in a subsequent article by Wilson and associates (2000), in which the relationship between outcome scales and other measures of outcome and clinical status was explored. The results suggest that both the GOS and GOSE show good agreement with injury severity, rating of disability, cognitive testing, perception of health, and symptoms reported by people with head injury and their relatives. In a similar vein, Levin and colleagues (2001) explored the relationship of the scales to functional and neuropsychological outcome measures. They found that the GOSE performed better than the GOS, a result that the authors believe will make the GOSE more sensitive than the GOS to interventions, especially when measuring changes over time.

In conclusion we recommend that the GOSE should be recorded in future studies, given the potential for increased sensitivity relative to the GOS. To realize this potential it is essential that ordinal analysis is used. Every effort should be taken to minimize inter-observer variability, including the use of structured interviews. Regular feedback and training sessions can serve to highlight the importance of taking great care to standardize the assessment of the GOSE.

This study can be seen as the final piece of the set of recommendations for trial conduct and analysis in TBI (Maas et al., 2010). In summary, we recommend that for future Phase III trials in TBI: (1) entry criteria should be broad, to include all patients who would be expected to benefit from the intervention being tested; (2) the analysis should be adjusted for key baseline covariates; (3) ordinal analysis should be used, based on either the proportional odds model or the sliding dichotomy; and (4) the GOSE should be used in preference to the GOS, since with an ordinal analysis this can yield a further modest but clinically-relevant increase in statistical efficiency that outweighs the additional effort required to assess the GOSE instead of the GOS.

Acknowledgments

This work was supported by the U.S. National Institutes of Health (Clinical Trial Design and Analysis in TBI Project: R01 NS-042691), and the U.K. Medical Research Council (Edinburgh Hub for Trials Methodology Research: G0800803).

Author Disclosure Statement

No competing financial interests exist.

References

- Altman, D.G., and Royston, P. (2006). The cost of dichotomising continuous variables. *BMJ* 332, 1080.
- Anderson, S.I., Housley, A.M., Jones, P.A., Slattery, J., and Miller, J.D. (1993). Glasgow Outcome Scale: an inter-rater reliability study. *Brain Inj.* 7, 309–317.
- Aoki, N., Kitahara, T., Fukui, T., Beck, J.R., Soma, K., Yamamoto, W., Kamae, I., and Ohwada, T. (1998). Management of unruptured intracranial aneurysm in Japan: A Markovian decision analysis with utility measurements based on the Glasgow Outcome Scale. *Med. Decis. Making* 18, 357–364.
- Bolland, K., Sooriyarachchi, M.R., and Whitehead, J. (1998). Sample size review in a head injury trial with ordered categorical responses. *Stat. Med.* 17, 2835–2847.
- Ford, I., and Norrie, J. (2002). The role of covariates in estimating treatment effects and risk in long-term clinical trials. *Stat. Med.* 21, 2899–2908.
- Gouvier, W.D., Blanton, P.D., and Kittle, K.S. (1986). Reliability and validity of the Expanded Glasgow Outcome Scale and the Stover-Zieger Scale. *Int. J. Clin. Neuropsychol.* 8, 1–2.
- Hall, K., Cope, D.N., and Rappaport, M. (1985). Glasgow Outcome Scale and Disability Rating Scale: comparative usefulness in following recovery in traumatic head injury. *Arch. Phys. Med. Rehabil.* 66, 35–37.
- Hernandez, A.V., Steyerberg, E.W., Butcher, I., Mushkudiani, N., Taylor, G.S., Murray, G.D., Marmarou, A., Choi, S.C., Lu, J., Habbema, J.D.F., and Maas, A.I.R. (2006). Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. *J. Neurotrauma* 23, 1295–1303.
- Horne, G., and Schemitsch, E. (1989). Assessment of the survivors of major trauma accidents. *Aust. N.Z. J. Surg.* 59, 465–470.
- Jennett, B., and Bond, M. (1975). Assessment of outcome after severe brain damage. *Lancet* 305, 480–484.
- Jennett, B., Snoek, J., Bond, M.R., and Brooks, N. (1981). Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *J. Neurol. Neurosurg. Psychiatry* 44, 285–293.
- Levin, H.S., Boake, C., Song, J., McCauley, S., Contant, C., Diaz-Marchan, P., Brundage, S., Goodman, H., and Kotrla, K.J. (2001). Validity and sensitivity to change of the extended Glasgow Outcome Scale in mild to moderate traumatic brain injury. *J. Neurotrauma* 18, 575–584.
- Livingston, M.G., and Livingston, H.M. (1985). The Glasgow Assessment Schedule: clinical and research assessment of head injury outcome. *Int. Rehabil. Med.* 7, 145–149.
- McCullagh, P. (1980). Regression models for ordinal data. *J. Royal Statistical Society Series B* 43, 109–142.
- McHugh, G.S., Butcher, I., Steyerberg, E.W., Marmarou, A., Lu, J., Lingsma, H.F., Weir, J., Maas, A.I., and Murray, G.D. (2010). A simulation study evaluating approaches to the analysis of ordinal outcome data in randomized controlled trials in traumatic brain injury: results from the IMPACT Project. *Clin. Trials* 7, 44–57.
- Maas, A.I., Braakman, R., Schouten, H.J., Minderhoud, J.M., and van Zomeren, A.H. (1983). Agreement between physicians on assessment of outcome following severe head injury. *J. Neurosurg.* 58, 321–325.
- Maas, A.I., Murray, G., Henney, H. III., Kassem, N., Legrand, V., Mangelus, M., Muizelaar, J.P., Stocchetti, N., and Knoller, N. (2006). Efficacy and safety of dexamethasone in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. *Lancet Neurol.* 5, 38–45.
- Maas, A.I., Steyerberg, E.W., Marmarou, A., McHugh, G.S., Lingsma, H.F., Butcher, I., Lu, J., Weir, J., Roozenbeek, B., and Murray, G.D. (2010). IMPACT recommendations for improving the design and analysis of clinical trials in moderate to severe traumatic brain injury. *Neurotherapeutics* 7, 127–134.

- Marmarou, A., Lu, J., Butcher, I., McHugh, G.S., Mushkudiani, N.A., Murray, G.D., Steyerberg, E.W., and Maas, A.I. (2007). IMPACT database of traumatic brain injury: design and description. *J. Neurotrauma* 24, 239–250.
- Murray, G.D., Butcher, I., McHugh, G.S., Lu, J., Mushkudiani, N.A., Maas, A.I., Marmarou, A., and Steyerberg, E.W. (2007). Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. *J. Neurotrauma* 24, 329–337.
- Robinson, L.D., and Jewell, N.P. (1991). Some surprising results about covariate adjustment in logistic regression models. *Int. Stat. Rev.* 59, 227–240.
- Sandset, E.C., Bath, P.M.W., Boysen, G., Jatuzis, D., K  rv, J., L  ders, S., Murray, G.D., Richter, P.S., Roine, R.O., Ter  nt, A., Thijs, V., and Berge, E., on behalf of the SCAST Study Group. (2011). The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 377, 741–750.
- Smith, R.M., Fields, F.R.J., Lenox, J.L., Morris, H.O., and Nolan, J.J. (1979). A functional scale of recovery from severe head trauma. *Clin. Neuropsychol.* 1, 48–50.
- Steyerberg, E.W., Mushkudiani, N., Perel, P., Butcher, I., Lu, J., McHugh, G.S., Murray, G.D., Marmarou, A., Roberts, I., Habbema, J.D.F., and Maas, A.I.R. (2008). Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS Med.* 5, e165.
- Teasdale, G.M., Murray, G.D., and Nicoll, J.A. (2005). The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. *Brain* 128, 2556–2561.
- Wilson, J.T., Pettigrew, L.E., and Teasdale, G.M. (2000). Emotional and cognitive consequences of head injury in relation to the Glasgow Outcome Scale. *J. Neurol. Neurosurg. Psychiatry* 69, 204–209.
- Wilson, J.T., Pettigrew, L.E., and Teasdale, G.M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J. Neurotrauma* 15, 573–585.

Address correspondence to:

Gordon D. Murray, Ph.D.

Centre for Population Health Sciences

University of Edinburgh Medical School

Teviot Place

Edinburgh EH8 9AG

Scotland, United Kingdom

E-mail: Gordon.Murray@ed.ac.uk